111/$1,030.00

Patent
Case No.: MJ 536

#6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Bristol-Myers Squibb Company
U.S. Patent No.: 4,338,317
Issue Date: July 6, 1982
For: Phenoxyethyl-1,2,4-Triazol-3-one Antidepressants
Inventors: Davis L. Temple Jr.; Walter G. Lobeck, Jr.

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Dear Sir:

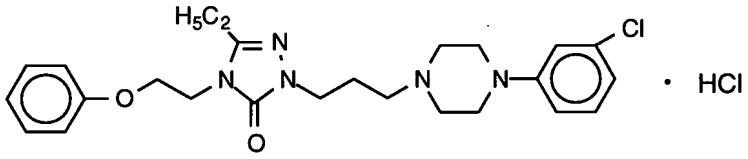
In accordance with the provisions of 35 USC 156, Bristol-Myers Squibb Company, a corporation of the state of Delaware, having a place of business at 5 Research Parkway, Wallingford, Connecticut 06492-7660, hereby applies for an extension of two years of the term of United States Patent No. 4,338,317 issued July 6, 1982.

The following items are relevant and follow the guidelines set forth by the United States Patent and Trademark Office Rules of Practice; 37 CFR §1.710, et seq.

1) This application for extension is based upon the regulatory review period before the Food and Drug Administration of SERZONE®. SERZONE is the trademark of Bristol-Myers Squibb Company for an antidepressant drug product having as its active ingredient nefazodone

hydrochloride. The package insert for SERZONE is enclosed herewith as Appendix 1.

Nefazodone hydrochloride is designated chemically as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one, hydrochloride salt, and has the following structure



2) Regulatory review of SERZONE occurred under Section 505 of the Federal Food, Drug and Cosmetic Act (21 USC 355).

3) SERZONE received permission for commercial marketing and use under Section 505 of the Federal Food, Drug and Cosmetic Act on December 22, 1994.

4) Nefazodone hydrochloride is the only active ingredient in SERZONE. Nefazodone hydrochloride has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

5) This application for extension of the term of United States Patent No. 4,338,317 is being submitted within the 60 day period permitted for submission pursuant to 37 CFR §1.720(f) beginning on December 22, 1994. The last day on which the application could be submitted is February 20, 1994.

6) This application for extension of patent term seeks to extend the term of United States Patent No. 4,338,317 issued July 6, 1982, which unless extended will expire on March 16, 2001, under provisions of the recently enacted Uruguay Round Agreements Act. This patent has not previously been extended.

The inventors named in the patent are Davis L. Temple, Jr. and Walter G. Lobeck, Jr. The patent is owned by Bristol-Myers Squibb Company by means of an assignment to a wholly-owned subsidiary, Mead Johnson and Company. The pertinent assignment was recorded on June 12, 1981 in the United States Patent and Trademark Office at Reel 3860, Frame 0473.

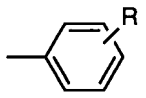
7) Attached hereto as Appendix 2 is a copy of United States Patent 4,338,317.

8) No disclaimers, certificates of correction, or reexamination certificates have been filed or issued in United States Patent No. 4,338,317. Copies of receipts for maintenance fee payments issued by the USPTO on January 6, 1986; January 6, 1990; and January 6, 1994 are attached as Appendix 3.

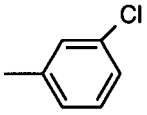
9) United States Patent No. 4,338,317 claims nefazodone hydrochloride, the active ingredient in SERZONE. The package insert for SERZONE shows that it is in tablet form. SERZONE is approved in tablet strengths of 50, 100, 200, 250 and 300 mg/tablet.

Claims 1 through 9 as allowed in United States Patent No. ,338,317 each include nefazodone hydrochloride within its scope. Note in particular the structural formula set out in Claim 1.

In Claim 1,

"  "

can be

"  ,

and a "pharmaceutically acceptable acid addition salt thereof" includes the hydrochloride salt. Thus, Claim 1 coverage of salts of nefazodone covers nefazodone hydrochloride. Claims 3, 6 and 9 specifically cover nefazodone hydrochloride, its antidepressant use, and its pharmaceutical compositions, respectively.

A description of each claim of U.S. Patent No. 4,338,317 follows.

Claim 1 of U.S. Patent No. 4,338,317 generically covers nefazodone, the active base ingredient of the approved product SERZONE and several closely related congeners and their pharmaceutical salts.

Claim 2 specifically covers the base form of nefazodone, the active ingredient in the approved product, SERZONE.

Claim 3 covers nefazodone hydrochloride, the salt form used in the approved product SERZONE.

Claim 4 covers the method of use of nefazodone and related compounds as given in Claim 1 for treating a mammal afflicted with depression.

Claim 5 covers the use of the free base form of nefazodone in the method of Claim 4.

Claim 6 covers the use of nefazodone hydrochloride according to the method of Claim 4.

Claim 7 covers a pharmaceutical composition comprising an antidepressant amount of a compound set forth in Claim 1.

Claim 8 covers a pharmaceutical composition comprising an antidepressant amount of the free base nefazodone according to the pharmaceutical composition of claim 7.

Claim 9 covers the pharmaceutical composition of claim 7 comprising an antidepressant amount of nefazodone hydrochloride.

10) The relevant dates and information pursuant to 35 USC 156(g) that will enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

For 35 USC 156(g)(1)(B)(i)-

The Notice of Claimed Investigational Exemption for a New Drug (IND number 20-993) for nefazodone hydrochloride, under the provisions of Section 505(i) of the Federal Food, Drug and Cosmetic Act, was filed on October 15, 1982, and became effective on November 17, 1982.

The New Drug Application (number 20-152) for SERZONE, under Section 505(b) of the Federal Food, Drug and Cosmetic Act, was filed on September 6, 1991.

For 35 USC 156(g)(1)(B)(ii)-

The New Drug Application (number 20-152) for SERZONE, under Section 505(b) of the Federal Food, Drug and Cosmetic Act, was filed on September 6, 1991.

The New Drug Application (number 20-152) for SERZONE, under Section 505(b) of the Federal Food, Drug and Cosmetic Act, was approved on December 22, 1994.

11) The following is a brief description of certain significant activities undertaken by Bristol-Myers Squibb Company during the applicable regulatory review period with respect to SERZONE including the dates applicable to such activities. Numerous other activities occurred which are not being listed here but are set forth in chronologies attached as Appendices 4 and 5. Continuing from the date of the final use in humans through the time of FDA approval, there were clinical studies in progress and/or being planned, with regular and frequent communications between Bristol-Myers Squibb Company and the FDA, and between Bristol-Myers Squibb Company and its clinical investigators.

October 15, 1982	-	Investigational New Drug Application 20-993 was filed. This provided for initial clinical studies under Protocol 030A2-001.
November 22, 1982	-	The first use in humans in the United States.
March 13, 1990	-	"End of Phase II" meeting is held with the FDA to discuss the further clinical development of nefazodone HCl.
February 11, 1991	-	"Pre-NDA" meeting is held to discuss content and format of proposed New Drug Application (NDA) for nefazodone HCl.
March 27, 1991	-	Meeting is held with FDA to discuss the manufacturing and controls sections of proposed NDA for nefazodone HCl.

September 6, 1991	-	New Drug Application for SERZONE (nefazodone HCl) is submitted.
January 7, 1992	-	FDA requests additional statistical analyses of data from certain placebo-controlled trials.
January 17, 1992	-	Safety Update No. 1 is submitted.
January 30, 1992	-	Meeting with FDA to discuss computer systems that will be provided in an effort to expedite the review of the NDA.
February 26, 1992	-	Additional statistical analyses requested on January 7, 1992 are submitted.
June 18, 1992	-	Teleconference is held with FDA to discuss, *inter alia*, response to request for additional statistical analyses.
July 19, 1993	-	Psychopharmacologic Drugs Advisory Committee discusses SERZONE and recommends approval.
October 28, 1992	-	Safety Update No. 2 is submitted.
November 7, 1994	-	FDA letter is received that indicates FDA has completed its review and concludes that SERZONE NDA is approvable.
November 17, 1994	-	BMS submits response to Approvable letter including additional safety data.
November 23, 1994	-	Revised draft labeling is submitted.

December 8, 1994 - Final labeling is negotiated with FDA at meeting.

December 22, 1994 - NDA No. 20-152 for SERZONE is approved.

12) It is the opinion of Bristol-Myers Squibb Company that United States No. 4,338,317 is eligible for a two-year extension of its term since:

(a) It claims the composition of matter of the active ingredient nefazodone hydrochloride, pharmaceutical compositions and antidepressant use of the approved human drug product, SERZONE;

(b) The term of said patent has never been previously extended;

(c) The application for extension of patent term is submitted by the owner of the patent, Bristol-Myers Squibb Company;

(d) The product, SERZONE, has been subject to regulatory review prior to commercial marketing or use;

(e) The product received permission for commercial marketing or use on December 22, 1994 and the application for patent term extension has been submitted within 60 days from that date;

(f) The term of the patent has not expired prior to this date of application; and

(g) No other patent term has been extended for the same regulatory review period for this product.

The length of extension claimed was determined in accordance with 35 USC §156(g) and 37 CFR §1.775(d). Since the subject patent, United States Patent No. 4,338,317 was issued prior to the 1984 enactment of §156 and the clinical investigation under IND 20-993 also commenced prior to the 1984 enactment date, the period of extension based on the regulatory review may not exceed two years.

The total extension time comprises one-half of the sum total of days of the testing and approval periods. In the present case, the pertinent dates are:

Patent issued:	July 6, 1982
Testing period began:	November 17, 1982
NDA submitted:	September 6, 1991
NDA approved:	December 22, 1994

Calculation of the total extension time pursuant to 37 CFR §1.775(d)(4) yields 2210 days according to the formula:

$$\frac{1}{2} \times \left[3215 \left(\begin{array}{c}\text{number of days from IND} \\ \text{to submission of NDA}\end{array} \right) + 1204 \left(\begin{array}{c}\text{number of days from NDA} \\ \text{submission to NDA approval}\end{array} \right) \right]$$

However, 37 CFR §1.775(d)(6)(ii)(A) applies and provides an extension period limited to two years. Since it is the earlier date which is to be applied, the extension period being sought therefore is for a two-year period.

13) Bristol-Myers Squibb Company and the undersigned acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

14) Authorization in accordance with 37 CFR §1.20(j) is given to charge the One Thousand Dollar ($1,000.00) fee for receiving and acting upon the application for extension to Deposit Account No. 02.3850. In the event the actual fee differs from this amount, it is requested that the overpayment or underpayment be credited or charged to Deposit Account No. 02.3850.

15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to this application for patent term extension should be directed is:

Richard P. Ryan
Bristol-Myers Squibb Company
P.O. Box 5100
Wallingford, CT 06492
Phone: 203-949-3723

16) A duplicate copy of this application, certified as such, is enclosed.

17) A signed declaration by a representative of Bristol-Myers Squibb Company is submitted herewith in compliance with 37 CFR 1.740(a)(17).

Respectfully submitted,

Dated: 19 Jan 95

Richard P. Ryan

Richard P. Ryan
Registration No. 30,491
Attorney for Applicants
Bristol-Myers Squibb Company
P. O. Box 5100
Wallingford, CT 06492-7660
Phone: (203) 949-3723

Patent
Case No.: MJ 536

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Bristol-Myers Squibb Company
U.S. Patent No.:	4,338,317
Issue Date:	July 6, 1982
For:	Phenoxyethyl-1,2,4-Triazol-3-one Antidepressants
Inventors:	Davis L. Temple Jr.; Walter G. Lobeck, Jr.

DECLARATION IN ACCORDANCE WITH 37 CFR §1.740(b)

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

I, Richard P. Ryan, residing at Middletown, Connecticut, declare as follows:

1. That I am an assistant patent counsel of Bristol-Myers Squibb Company, a corporation of the state of Delaware, having a place of business at 5 Research Parkway, Wallingford, Connecticut 06492-7660; I am an attorney registered to practice in the United States Patent and Trademark Office under registration no. 30,491 and I have general authority from Bristol-Myers Squibb Company to act on its behalf in patent matters.

2. That Bristol-Myers Squibb Company is the owner of the entire right, title and interest in United States Patent No. 4,338,317.

3. That I have reviewed and understand the contents of the Application for Extension of Patent Term Under 35 USC 156 for United States Patent No. 4,338,317 which is submitted herewith.

4. That I believe that the above-identified patent is subject to an extension pursuant to 37 CFR §1.710.

5. That I believe that a two-year extension of the term of the patent is fully justified under 35 USC 156 and the applicable regulations.

6. That I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR §1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application for extension of patent term and the validity of United States Patent No. 4,338,317.

Respectfully submitted,

Dated: 19 Jan 95

Richard P. Ryan

Richard P. Ryan
Registration No. 30,491
Attorney for Applicants
Bristol-Myers Squibb Company
P. O. Box 5100
Wallingford, CT 06492-7660
Phone: (203) 949-3723

MJ 536
RPR

Inventors: Davis L. Temple Jr.; Walter G. Lobeck, Jr.
Applicant: Bristol-Myers Squibb Company
U.S. Patent No.: 4,338,317
Issue Date: July 6, 1982
For: PHENOXYETHYL-1,2,4-TRIAZOL-3-ONE ANTIDEPRESSANTS

1) Application for Extension of Patent Term Under 35 U.S.C. 156, with attachments

   (i) Declaration
   (ii) SERZONE® Package Insert (Appendix 1)
   (iii) U.S. Patent 4,338,317 (Appendix 2)
   (iv) Receipts for maintenance fee payments (Appendix 3)
   (v) Chronology - Post IND Activities (Appendix 4)
   (vi) Chronology - NDA Activities (Appendix 5)

2) Certified copy of above

3) Three courtesy copies of above

APPENDIX 1

SERZONE® package insert

P4460-00

SERZONE®
(nefazodone hydrochloride)
Tablets

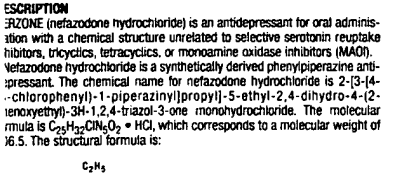
Bristol-Myers Squibb Company

AUTION: Federal law prohibits dispensing without prescription.

SERZONE®
nefazodone hydrochloride)
ablets

ESCRIPTION

ERZONE (nefazodone hydrochloride) is an antidepressant for oral adminis-ation with a chemical structure unrelated to selective serotonin reuptake hibitors, tricyclics, tetracyclics, or monoamine oxidase inhibitors (MAOI). lefazodone hydrochloride is a synthetically derived phenylpiperazine anti-epressant. The chemical name for nefazodone hydrochloride is 2-[3-[4--chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-enoxyethyl)-3H-1,2,4-triazol-3-one monohydrochloride. The molecular rmula is $C_{25}H_{32}ClN_5O_2 \cdot HCl$, which corresponds to a molecular weight of 06.5. The structural formula is:



lefazodone hydrochloride is a nonhygroscopic, white crystalline solid. It is ely soluble in chloroform, soluble in propylene glycol, and slightly soluble polyethylene glycol and water.

ERZONE is supplied as hexagonal tablets containing 100 mg, 150 mg, 200 mg, or 250 mg of nefazodone hydrochloride and the following inactive ingredients: microcrystalline cellulose, povidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and iron oxides (red and/or yellow) as colorants.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of nefazodone, as with other antidepressants, is unknown.

Preclinical studies have shown that nefazodone inhibits neuronal uptake of serotonin and norepinephrine.

Nefazodone occupies central 5-HT_2 receptors at nanomolar concentrations, and acts as an antagonist at this receptor. Nefazodone was shown to antagonize alpha$_1$-adrenergic receptors, a property which may be associated with postural hypotension. *In vitro* binding studies showed that nefazodone had no significant affinity for the following receptors: alpha$_2$ and beta adrenergic, 5-HT_{1A}, cholinergic, dopaminergic, or benzodiazepine.

Pharmacokinetics

Nefazodone hydrochloride is rapidly and completely absorbed but is subject to extensive metabolism, so that its absolute bioavailability is low, about 20%, and variable. Peak plasma concentrations occur at about one hour and the half-life of nefazodone is 2–4 hours.

Both nefazodone and its pharmacologically similar metabolite, hydroxynefazodone, exhibit nonlinear kinetics for both dose and time, with AUC and C_{max} increasing more than proportionally with dose increases and more than expected upon multiple dosing over time, compared to single dosing. For example, in a multiple-dose study involving BID dosing with 50, 100, and 200 mg, the AUC for nefazodone and hydroxynefazodone increased by about 4-fold with an increase in dose from 200 to 400 mg per day; C_{max} increased by about 3-fold with the same dose increase. In a multiple-dose study involving BID dosing with 25, 50, 100, and 150 mg, the accumulation ratios for nefazodone and hydroxynefazodone AUC, after 5 days of BID dosing relative to the first dose, ranged from approximately 3 to 4 at the lower doses (50–100 mg/day) and from 5 to 7 at the higher doses (200–300 mg/day); there were also approximately 2- to 4-fold increases in C_{max} after 5 days of BID dosing relative to the first dose, suggesting extensive and greater than predicted accumulation of nefazodone and its hydroxy metabolite with multiple dosing. Steady-state plasma nefazodone and metabolite concentrations are attained within 4 to 5 days of initiation of BID dosing or upon dose increase or decrease.

Nefazodone is extensively metabolized after oral administration by n-dealkylation and aliphatic and aromatic hydroxylation, and less than 1% of administered nefazodone is excreted unchanged in urine. Attempts to characterize three metabolites identified in plasma, hydroxynefazodone (HO-NEF), metachlorophenylpiperazine (mCPP), and a triazole-dione metabolite, have been carried out. The AUC (expressed as a multiple of the AUC for nefazodone dosed at 100 mg BID) and elimination half-lives for these three metabolites were as follows:

AUC Multiples and T1/2 for Three Metabolites of Nefazodone (100 mg BID)

Metabolite	AUC Multiple	T1/2
HO-NEF	0.4	1.5–4 hrs
mCPP	0.07	4–8 hrs
Triazole-dione	4.0	18 hrs

HO-NEF possesses a pharmacological profile qualitatively and quantitatively similar to that of nefazodone. mCPP has some similarities to nefazodone, but also has agonist activity at some serotonergic receptor subtypes. The pharmacological profile of the triazole-dione metabolite has not yet been well characterized. In addition to the above compounds, several other metabolites were present in plasma but have not been tested for pharmacological activity.

After oral administration of radiolabelled nefazodone, the mean half-life of total label ranged between 11 and 24 hours. Approximately 55% of the administered radioactivity was detected in urine and about 20–30% in feces.

Distribution—Nefazodone is widely distributed in body tissues, including the central nervous system (CNS). In humans the volume of distribution of nefazodone ranges from 0.22 to 0.87 l/kg.

Protein Binding—At concentrations of 25–2500 ng/mL nefazodone is extensively (>99%) bound to human plasma proteins *in vitro*. While nefazodone did not alter the *in vitro* protein binding of chlorpromazine, desipramine, diazepam, diphenylhydantoin, lidocaine, prazosin, propranolol, verapamil, or warfarin, it is unknown whether or not displacement of either nefazodone or other drugs occurs *in vivo*. There was a 5% decrease in the protein binding of haloperidol; this is probably of no clinical significance.

Effect of Food—Food delays the absorption of nefazodone and decreases the bioavailability of nefazodone by approximately 20%.

Renal Disease—In studies involving 29 renally impaired patients, renal impairment (creatinine clearances ranging from 7 to 60 mL/min/1.73m^2) had no effect on steady-state nefazodone plasma concentrations.

Liver Disease—In a multiple-dose study of patients with liver cirrhosis, the AUC values for nefazodone and HO-NEF at steady state were approximately 25% greater than those observed in normal volunteers.

Age/Gender Effects—After single doses of 300 mg to younger and older patients, C_{max} and AUC for nefazodone and hydroxynefazodone were up to twice as high in the older patients. With multiple doses, however, differences were much smaller, 10–20%. A similar result was seen for gender, with a higher C_{max} and AUC in women after single doses but no difference after multiple doses.

Treatment with SERZONE should be initiated at half the usual dose in elderly patients, especially women (see **DOSAGE AND ADMINISTRATION** Section), but the therapeutic dose range is similar in younger and older patients.

Clinical Trials Supporting the Effectiveness Claim

The efficacy of SERZONE (nefazodone hydrochloride) as a treatment for depression was established in two placebo-controlled, short-term trials in outpatients meeting DSM-III or DSM-IIIR criteria for major depression. One was a 6-week dose-titration study comparing SERZONE in two dose ranges (up to 300 mg/day and up to 600 mg/day [mean modal dose for this group was about 400 mg/day], on a BID schedule) and placebo. The other was an 8-week dose-titration study comparing SERZONE (up to 600 mg/day; mean modal dose was 375 mg/day), imipramine (up to 300 mg/day), and placebo, all on a BID schedule. Overall, these studies demonstrated SERZONE, at doses titrated up to 600 mg/day, to be superior to placebo on at least three of the following four measures: 17-item Hamilton Depression Rating Scale or HDRS (total score), Hamilton Depressed Mood item, CGI Severity score, and CGI Improvement score. Significant differences were also found for certain factors of the HDRS (e.g., anxiety factor, sleep disturbance factor, and retardation factor). Two other 6-8 week placebo- and imipramine-controlled studies in depressed outpatients provided additional support for the superiority of nefazodone (titrated up to 500 or 600 mg/day; mean modal doses of 462 mg/day and 363 mg/day) over placebo.

There were no efficacy studies focusing specifically on the elderly or on men and women separately. Overall, approximately two-thirds of patients in these trials were women, and an analysis of the effects of gender on outcome did not suggest any differential responsiveness on the basis of sex. There were too few elderly patients in these trials to reveal possible age-related differences in response.

INDICATIONS AND USAGE

SERZONE (nefazodone hydrochloride) is indicated for the treatment of depression.

The efficacy of SERZONE in the treatment of depression was established in 6-8 week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III or DSM-IIIR category of major depressive disorder (see **CLINICAL PHARMACOLOGY** Section).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it must include either depressed mood or loss of interest or pleasure and at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of SERZONE in hospitalized depressed patients has not been adequately studied.

The effectiveness of SERZONE in long-term use, that is, for more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SERZONE for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Coadministration of terfenadine or astemizole with SERZONE (nefazodone hydrochloride) is contraindicated (see **WARNINGS** and **PRECAUTIONS** Sections).

SERZONE is contraindicated in patients with known hypersensitivity to nefazodone or other phenylpiperazine antidepressants.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving antidepressants with pharmacological properties similar to nefazodone in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI.

Although the effects of combined use of nefazodone and MAOI have not been evaluated in humans or animals, because nefazodone is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that nefazodone not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 1 week should be allowed after stopping nefazodone before starting a MAOI.

Interaction with Triazolobenzodiazepines

Interaction studies of nefazodone with two triazolobenzodiazepines, i.e., triazolam and alprazolam, metabolized by cytochrome P_{450}IIIA$_4$, have revealed substantial and clinically important increases in plasma concentrations of these compounds when administered concomitantly with nefazodone.

Triazolam

When a single oral 0.25-mg dose of triazolam was coadministered with nefazodone (200 mg BID) at steady state, triazolam half-life and AUC increased 4-fold and peak concentrations increased 1.7-fold. Nefazodone plasma concentrations were unaffected by triazolam. ***Coadministration of nefazodone potentiated the effects of triazolam on psychomotor performance tests.*** If triazolam is coadministered with SERZONE, a 75% reduction in the initial triazolam dosage is recommended. For many patients, e.g., the elderly, it is recommended that triazolam not be used in combination with nefazodone. No dosage adjustment is required for SERZONE.

Alprazolam

When alprazolam (1 mg BID) and nefazodone (200 mg BID) were coadministered, steady-state peak concentrations, AUC and half-life values for alprazolam increased by approximately 2-fold. Nefazodone plasma concentrations were unaffected by alprazolam. If alprazolam is coadministered with SERZONE, a 50% reduction in the initial alprazolam dosage is recommended. No dosage adjustment is required for SERZONE.

Potential Terfenadine and Astemizole Interactions

Terfenadine and astemizole are both metabolized by the cytochrome P_{450}IIIA$_4$ isozyme, and it has been demonstrated that ketoconazole, erythromycin, and other inhibitors of IIIA$_4$ can block the metabolism of terfenadine and astemizole, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine and astemizole are associated with QT prolongation and with rare cases of serious cardiovascular adverse events, including death, due principally to ventricular tachycardia of the torsades de pointes type. Nefazodone has been shown *in vitro* to be an inhibitor of IIIA$_4$. Consequently, it is recommended that nefazodone not be used in combination with either terfenadine or astemizole (see CONTRAINDICATIONS and PRECAUTIONS Sections).

PRECAUTIONS

General

Postural Hypotension

A pooled analysis of the vital signs monitored during placebo-controlled premarketing studies revealed that 5.1% of nefazodone patients compared to 2.5% of placebo patients ($p \leq 0.01$) met criteria for a potentially important decrease in blood pressure at some time during treatment (systolic blood pressure ≤90 mmHg *and* a change from baseline of ≥20 mmHg). While there was no difference in the proportion of nefazodone and placebo patients having adverse events characterized as 'syncope' (nefazodone, 0.2%; placebo, 0.3%), the rates for adverse events characterized as 'postural hypotension' were as follows: nefazodone (2.8%), tricyclic antidepressants (10.9%), SSRI (1.1%), and placebo (0.8%). Thus, the prescriber should be aware that there is some risk of postural hypotension in association with nefazodone use. SERZONE should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in 0.3% of nefazodone-treated unipolar patients, compared to 0.3% of tricyclic- and 0.4% of placebo-treated patients. In patients classified as bipolar the rate of manic episodes was 1.6% for nefazodone, 5.1% for the combined tricyclic-treated groups, and 0% for placebo-treated patients. Activation of mania/hypomania is a known risk in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, SERZONE (nefazodone hydrochloride) should be used cautiously in patients with a history of mania.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for SERZONE should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Seizures

During premarketing testing, a recurrence of a petit mal seizure was observed in a patient receiving nefazodone who had a history of such seizures. One nonstudy participant took 2000–3000 mg of nefazodone with methocarbamol and alcohol; this person reportedly experienced a convulsion (type not documented).

Priapism

While priapism did not occur during premarketing experience with nefazodone, priapism has been reported with a structurally related drug, trazodone. If patients present with prolonged or inappropriate erections, they should discontinue therapy immediately and consult their physicians. If the condition persists for more than 24 hours, a urologist should be consulted to determine appropriate management.

Use in Patients with Concomitant Illness

SERZONE has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. Evaluation of electrocardiograms of 1153 patients who received nefazodone in 6- to 8-week, double-blind, placebo-controlled trials did not indicate that nefazodone is associated with the development of clinically important ECG abnormalities. However, sinus bradycardia, defined as heart rate ≤50 bpm and a decrease of at least 15 bpm from baseline, was observed in 1.5% of nefazodone-treated patients compared to 0.4% of placebo-treated patients ($p \leq 0.05$). Because patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical trials, such patients should be treated with caution.

In patients with cirrhosis of the liver, the AUC values of nefazodone and HO-NEF were increased by approximately 25%.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SERZONE:

Time to Response/Continuation

As with all antidepressants, several weeks on treatment may be required to obtain the full antidepressant effect. Once improvement is noted, it is important for patients to continue drug treatment as directed by their physician.

Interference With Cognitive and Motor Performance

Since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SERZONE therapy does not adversely affect their ability to engage in such activities.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised to notify their physician if they are bre... ing an infant (see **PRECAUTIONS** Section, **Nursing Mothers** Sub...

Concomitant Medication

Patients should be advised to inform their physicians if they are t... plan to take, any prescription or over-the-counter drugs, since t... potential for interactions. Significant caution is indicated if SERZ... be used in combination with either Halcion or Xanax, and concomit... with Seldane or Hismanal is contraindicated (see **CONTRAINDI...** and **WARNINGS** Sections).

Alcohol

Patients should be advised to avoid alcohol while taking SERZONE...

Allergic Reactions

Patients should be advised to notify their physician if they develo... hives, or a related allergic phenomenon.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Drugs Highly Bound to Plasma Protein

Because nefazodone is highly bound to plasma protein (see **CLINICAL PHARMACOLOGY** Section, **Pharmacokinetics** Subsection), administ... SERZONE to a patient taking another drug that is highly protein bo... cause increased free concentrations of the other drug, potentially ... in adverse events. Conversely, adverse effects could result from ... ment of nefazodone by other highly bound drugs.

CNS Active Drugs

Monoamine Oxidase Inhibitors—See **WARNINGS** Section

Haloperidol—When a single oral 5-mg dose of haloperidol was co... tered with nefazodone (200 mg BID) at steady state, haloperidol ... clearance decreased by 35% with no significant increase in peak ... dol plasma concentrations or time of peak. This change is unlikely ... ical significance. Pharmacodynamic effects of haloperidol were ... not altered significantly. There were no changes in the pharmac... parameters for nefazodone. Dosage adjustment of haloperidol may ... essary when coadministered with nefazodone.

Lorazepam—When lorazepam (2 mg BID) and nefazodone (200 ... were coadministered to steady state, there was no change in a... macokinetic parameter for either drug compared to each drug ... tered alone. Therefore, dosage adjustment is not necessary ... drug when coadministered.

Triazolam/Alprazolam—See **WARNINGS** Section

Alcohol—Although nefazodone did not potentiate the cognitive ... chomotor effects of alcohol in experiments with normal subjects, ... comitant use of SERZONE and alcohol in depressed patients is not ...

General Anesthetics—Little is known about the potential for in... between nefazodone and general anesthetics; therefore, prior to ... surgery, SERZONE should be discontinued for as long as clinically ...

Other CNS Active Drugs—The use of nefazodone in combination w... CNS-active drugs has not been systematically evaluated. Consi... caution is advised if concomitant administration of SERZONE a... drugs is required.

Cimetidine

When nefazodone (200 mg BID) and cimetidine (300 mg QID) we... ministered for one week, no change in the steady-state pharmac... of either nefazodone or cimetidine was observed compared to ea... alone. Therefore, dosage adjustment is not necessary for either dr... coadministered.

Cardiovascular Active Drugs

Digoxin—When nefazodone (200 mg BID) and digoxin (0.2 mg ... coadministered for 9 days to healthy male volunteers (n=18) w... phenotyped as P_{450}IID$_6$ extensive metabolizers, C_{max}, C_{min}, and ... digoxin were increased by 29%, 27%, and 15%, respectively. Dig... no effects on the pharmacokinetics of nefazodone and its active ... lites. Because of the narrow therapeutic index of digoxin, caution s... exercised when nefazodone and digoxin are coadministered; plas... monitoring for digoxin is recommended.

Propranolol—The coadministration of nefazodone (200 mg BID) ... pranolol (40 mg BID) for 5.5 days to healthy male volunteers (n=18 ... ing 3 poor and 15 extensive P_{450}IID$_6$ metabolizers, resulted in ... 14% reductions in C_{max} and AUC of propranolol, respectively, and ... reduction in C_{max} for the metabolite, 4-hydroxypropranolol. The ki... nefazodone, hydroxynefazodone, and triazole-dione were not affe... coadministration of propranolol. However, C_{max}, C_{min}, and AUC ... chlorophenylpiperazine were increased by 23%, 54%, and 22%, ... tively. No change in initial dose of either drug is necessary and dose ... ments should be made on the basis of clinical response.

Pharmacokinetics of Nefazodone in 'Poor Metabolizers' and Interaction with Drugs That Inhibit and/or are Metabolized by Cyt... P_{450} Isozymes

IIIA$_4$ Isozyme— Nefazodone has been shown *in vitro* to be an inh... cytochrome P_{450}IIIA$_4$. This is consistent with the interaction observed ... nefazodone and the benzodiazepines triazolam and alprazolam, drugs ... olized by this isozyme. Consequently, caution is indicated in the comb... of nefazodone with any drugs known to be metabolized by the IIIA$_4$ ... In particular, the combined use of nefazodone with either terfenadine ... izole is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS** S...

IID$_6$ Isozyme—A subset (3% to 10%) of the population has reduced ... of the drug-metabolizing enzyme cytochrome P_{450}IID$_6$. Such individ... referred to commonly as "poor metabolizers" of drugs such as debr... dextromethorphan, and the tricyclic antidepressants. The pharmac...

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metabolizers.* Plasma concentrations of one minor metabolite (mCPP) are increased in this population, the adjustment of SERZONE dosage is not required when administered to "poor metabolizers." Nefazodone and its metabolites have been shown *in vitro* to be extremely weak inhibitors of $P_{450}IID_6$. Thus, it is not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme.

IA_2 Isozyme—Nefazodone and its metabolites have been shown *in vitro* not to inhibit cytochrome $P_{450}IA_2$. Thus, metabolic interactions between nefazodone and drugs metabolized by this isozyme are unlikely.

Electro-Convulsive Therapy (ECT)
There are no clinical studies of the combined use of ECT and nefazodone.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
There is no evidence of carcinogenicity with nefazodone. The dietary administration of nefazodone to rats and mice for 2 years at daily doses of up to 200 mg/kg and 800 mg/kg, respectively, which are approximately 3 and 6 times, respectively, the maximum human daily dose on a mg/m^2 basis, produced no increase in tumors.

Mutagenesis
Nefazodone has been shown to have no genotoxic effects based on the following assays: bacterial mutation assays, a DNA repair assay in cultured rat hepatocytes, a mammalian mutation assay in Chinese hamster ovary cells, an *in vivo* cytogenetics assay in rat bone marrow cells, and a rat dominant lethal study.

Impairment of Fertility
A fertility study in rats showed a slight decrease in fertility at 200 mg/kg/day (approximately three times the maximum human daily dose on a mg/m^2 basis) but not at 100 mg/kg/day (approximately 1.5 times the maximum human daily dose on a mg/m^2 basis).

Pregnancy
Teratogenic Effects—Pregnancy Category C
Reproduction studies have been performed in pregnant rabbits and rats at daily doses up to 200 and 300 mg/kg, respectively (approximately 6 and 5 times, respectively, the maximum human daily dose on a mg/m^2 basis). No malformations were observed in the offspring as a result of nefazodone treatment. However, increased early pup mortality was seen in rats at a dose approximately 5 times the maximum human dose, and decreased pup weights were seen at this and lower doses when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 1.3 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Nefazodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of SERZONE on labor and delivery in humans is unknown.

Nursing Mothers
It is not known whether SERZONE or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SERZONE is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in individuals below 18 years of age have not been established.

Geriatric Use
Of 500 elderly (≥65 years) individuals participated in clinical studies with nefazodone, no unusual adverse age-related phenomena were identified. In a cohort of elderly patients treated with nefazodone. Due to the increased systemic exposure to nefazodone seen in single dose studies in elderly patients (see **CLINICAL PHARMACOLOGY** Section, **Pharmacokinetics** Subsection), treatment should be initiated at half the usual dose, but titration upward should take place over the same range as in younger patients (see **DOSAGE AND ADMINISTRATION** Section). The usual precautions should be observed in elderly patients who have concomitant medical illnesses or who are receiving concomitant drugs.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment
Approximately 16% of the 3496 patients who received SERZONE (nefazodone hydrochloride) in worldwide premarketing clinical trials discontinued treatment due to an adverse experience. The more common (≥1%) events in clinical trials associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for SERZONE compared to placebo) included: nausea (3.5%), dizziness (1.9%), insomnia (1.5%), asthenia (1.3%), and agitation (1.2%).

Incidence in Controlled Trials
Commonly Observed Adverse Events in Controlled Clinical Trials:
The most commonly observed adverse events associated with the use of SERZONE (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., significantly higher incidence for SERZONE compared to placebo, p≤0.05), derived from the table below, were: somnolence, dry mouth, nausea, dizziness, constipation, asthenia, lightheadedness, blurred vision, confusion, and abnormal vision.

Adverse Events Occurring at an Incidence of 1% or More Among SERZONE-Treated Patients
The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among SERZONE-treated patients who participated in short-term (6- to 8-week) placebo-controlled trials in which patients were dosed with SERZONE to ranges of 300 to 600 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Placebo-Controlled Clinical Trials[1]
SERZONE 300 to 600 mg/day Dose Range

Body System	Preferred Term	SERZONE (n=393)	Placebo (n=394)
Body as a Whole	Headache	36%	33%
	Asthenia	11%	5%
	Infection	8%	6%
	Flu syndrome	3%	2%
	Chills	2%	1%
	Fever	2%	1%
	Neck Rigidity	1%	0
Cardiovascular	Postural hypotension	4%	1%
	Hypotension	2%	1%
Dermatological	Pruritus	2%	1%
	Rash	2%	1%
Gastrointestinal	Dry mouth	25%	13%
	Nausea	22%	12%
	Constipation	14%	8%
	Dyspepsia	9%	7%
	Diarrhea	8%	7%
	Increased appetite	5%	3%
	Nausea & Vomiting	2%	1%
Metabolic	Peripheral edema	3%	2%
	Thirst	1%	<1%
Musculoskeletal	Arthralgia	1%	<1%
Nervous	Somnolence	25%	14%
	Dizziness	17%	5%
	Insomnia	11%	9%
	Lightheadedness	10%	3%
	Confusion	7%	2%
	Memory impairment	4%	2%
	Paresthesia	4%	2%
	Vasodilatation[2]	4%	2%
	Abnormal dreams	3%	2%
	Concentration decreased	3%	1%
	Ataxia	2%	0
	Incoordination	2%	1%
	Psychomotor retardation	2%	1%
	Tremor	2%	1%
	Hypertonia	1%	0
	Libido decreased	1%	<1%
Respiratory	Pharyngitis	6%	5%
	Cough increased	3%	1%
Special Senses	Blurred vision	9%	3%
	Abnormal vision[3]	7%	1%
	Tinnitus	2%	1%
	Taste perversion	2%	1%
	Visual field defect	2%	0
Urogenital	Urinary frequency	2%	1%
	Urinary tract infection	2%	1%
	Urinary retention	2%	1%
	Vaginitis[4]	2%	1%
	Breast pain[4]	1%	<1%

[1] Events reported by at least 1% of patients treated with SERZONE and more frequent than the placebo group are included; incidence is rounded to the nearest 1% (<1% indicates an incidence less than 0.5%). Events for which the SERZONE incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, accidental injury, chest pain, neck pain, palpitation, migraine, sweating, flatulence, vomiting, anorexia, tooth disorder, weight gain, edema, myalgia, cramp, agitation, anxiety, depression, hypesthesia, CNS stimulation, dysphoria, emotional lability, sinusitis, rhinitis, dysmenorrhea[4], dysuria.
[2] Vasodilatation—flushing, feeling warm.
[3] Abnormal vision—scotoma, visual trails
[4] Incidence adjusted for gender.

Dose Dependency of Adverse Events
The table that follows enumerates adverse events that were more frequent in the SERZONE dose range of 300 to 600 mg/day than in the SERZONE dose range of up to 300 mg/day. This table shows only those adverse events for which there was a statistically significant difference (p≤0.05) in incidence between the SERZONE dose ranges as well as a difference between the high dose range and placebo.

Dose Dependency of Adverse Events in Placebo-Controlled Trials[1]

Body System	Preferred Term	SERZONE 300-600 mg/day (n = 209)	SERZONE ≤300 mg/day (n = 211)	Placebo (n = 212)
Gastrointestinal	Nausea	23%	14%	12%
	Constipation	17%	10%	9%
Nervous	Somnolence	28%	16%	13%
	Dizziness	22%	11%	4%
	Confusion	8%	2%	1%
Special Senses	Abnormal vision	10%	0	2%
	Blurred vision	9%	3%	2%
	Tinnitus	3%	0	1%

[1] Events for which there was a statistically significant difference (p≤0.05) between the nefazodone dose groups.

(See **PRECAUTIONS** Section, *Postural Hypotension* Subsection)

Weight Changes
In a pooled analysis of placebo-controlled premarketing studies, there were no differences between nefazodone and placebo groups in the proportions of patients meeting criteria for potentially important increases or decreases in body weight (a change of ≥7%).

Laboratory Changes:
Of the serum chemistry, serum hematology, and urinalysis parameters monitored during placebo-controlled premarketing studies with nefazodone, a pooled analysis revealed a statistical trend between nefazodone and placebo for hematocrit, i.e., 2.8% of nefazodone patients met criteria for a potentially important decrease in hematocrit (≤37% male or ≤32% female) compared to 1.5% of placebo patients (0.05<p≤0.10). Decreases in hematocrit, presumably dilutional, have been reported with many other drugs that block alpha$_1$-adrenergic receptors. There was no apparent clinical significance of the observed changes in the few patients meeting these criteria.

ECG Changes
Of the ECG parameters monitored during placebo-controlled premarketing studies with nefazodone, a pooled analysis revealed a statistically significant difference between nefazodone and placebo for sinus bradycardia, i.e., 1.5% of nefazodone patients met criteria for a potentially important decrease in heart rate (≤50 bpm and a decrease of ≥15 bpm) compared to 0.4% of placebo patients (p<0.05). There was no obvious clinical significance of the observed changes in the few patients meeting these criteria.

Other Events Observed During the Premarketing Evaluation of SERZONE
During its premarketing assessment, multiple doses of SERZONE were administered to 3496 patients in clinical studies, including more than 250 patients treated for at least one year. The conditions and duration of exposure to SERZONE varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 3496 patients exposed to multiple doses of SERZONE who experienced an event of the type cited on at least one occasion while receiving SERZONE. All reported events are included except those already listed in the Treatment-Emergent Adverse Experience Incidence table, those events listed in other safety-related sections of this insert, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events for which a drug cause was very remote, and those events which were not serious and occurred in fewer than two patients.

It is important to emphasize that, although the events reported occurred during treatment with SERZONE, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a whole—Infrequent: allergic reaction, malaise, photosensitivity reaction, face edema, hangover effect, abdomen enlarged, hernia, pelvic pain, and halitosis. *Rare:* cellulitis.

Cardiovascular system—Infrequent: tachycardia, hypertension, syncope, ventricular extrasystoles, and angina pectoris. *Rare:* AV block, congestive heart failure, hemorrhage, pallor, and varicose vein.

Dermatological system—Infrequent: dry skin, acne, alopecia, urticaria, maculopapular rash, vesiculobullous rash, and eczema.

Gastrointestinal system—Frequent: gastroenteritis. *Infrequent:* eructation, periodontal abscess, abnormal liver function tests, gingivitis, colitis, gastritis, mouth ulceration, stomatitis, esophagitis, peptic ulcer, and rectal hemorrhage. *Rare:* glossitis, hepatitis, dysphagia, gastrointestinal hemorrhage, oral moniliasis, and ulcerative colitis.

Hemic and lymphatic system—Infrequent: ecchymosis, anemia, leukopenia, and lymphadenopathy.

Metabolic and nutritional system—Infrequent: weight loss, gout, dehydration, lactic dehydrogenase increased, SGOT increased, and SGPT increased. *Rare:* hypercholesteremia and hypoglycemia.

Musculoskeletal system—Infrequent: arthritis, tenosynovitis, muscle stiffness, and bursitis. *Rare:* tendinous contracture.

Nervous system—Infrequent: vertigo, twitching, depersonalization, hallucinations, suicide attempt, apathy, euphoria, hostility, suicidal thoughts, abnormal gait, thinking abnormal, attention decreased, derealization, neuralgia, paranoid reaction, dysarthria, increased libido, sucidal, and myoclonus. *Rare:* hyperkinesia, increased salivation, cerebrovascular accident, hyperesthesia, hypotonia, ptosis, and neuroleptic malignant syndrome.

Respiratory system—Frequent: dyspnea and bronchitis. *Infrequent:* asthma, pneumonia, laryngitis, voice alteration, epistaxis, hiccup. *Rare:* hyperventilation and yawn.

Special senses—Frequent: eye pain. *Infrequent:* dry eye, ear pain, abnormality of accommodation, diplopia, conjunctivitis, mydriasis, keratoconjunctivitis, hyperacusis, and photophobia. *Rare:* deafness, glaucoma, night blindness, and taste loss.

urgency, metrorrhagia[4], amenorrhea[4], polyuria, vaginal hemorrhage[4], breast enlargement[4], menorrhagia[4], urinary incontinence, abnormal ejaculation[4], hematuria, nocturia, and kidney calculus. *Rare:* uterine fibroids enlarged[4], uterine hemorrhage[4], anorgasmia, and oliguria.

[4]Adjusted for gender.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class
SERZONE (nefazodone hydrochloride) is not a controlled substance.

Physical and Psychological Dependence
In animal studies, nefazodone did not act as a reinforcer for intravenous self-administration in monkeys trained to self-administer cocaine, suggesting no abuse liability. In a controlled study of abuse liability in human subjects, nefazodone showed no potential for abuse.

Nefazodone has not been systematically studied in humans for its potential for tolerance, physical dependence, or withdrawal. While the premarketing clinical experience with nefazodone did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SERZONE (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Human Experience
There is very limited experience with nefazodone overdose. In premarketing clinical studies, there were seven reports of nefazodone overdose alone or in combination with other pharmacological agents. The amount of nefazodone ingested ranged from 1000 mg to 11,200 mg. Commonly reported symptoms from overdose of nefazodone included nausea, vomiting, and somnolence. One nonstudy participant took 2000–3000 mg of nefazodone with methocarbamol and alcohol; this person reportedly experienced a convulsion (type not documented). None of the patients died.

Overdose Management
Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions (see **ADVERSE REACTIONS** Section).

There is no specific antidote for SERZONE (nefazodone hydrochloride). Treatment should be symptomatic and supportive in the case of hypotension or excessive sedation. Any patient suspected of having taken an overdose should have the stomach emptied by gastric lavage.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment
The recommended starting dose for SERZONE (nefazodone hydrochloride) is 200 mg/day, administered in two divided doses (BID). In the controlled clinical trials establishing the antidepressant efficacy of SERZONE, the effective dose range was generally 300 to 600 mg/day. Consequently, most patients, depending on tolerability and the need for further clinical effect, should have dose increased. Dose increases should occur in increments of 100 mg/day to 200 mg/day, again on a BID schedule, at intervals of no less than 1 week. As with all antidepressants, several weeks on treatment may be required to obtain a full antidepressant response.

Dosage for Elderly or Debilitated Patients
The recommended initial dose for elderly or debilitated patients is 100 mg/day on a BID schedule. These patients often have reduced nefazodone clearance and/or increased sensitivity to the side effects of CNS-active drugs. It may also be appropriate to modify the rate of subsequent dose titration. As steady-state plasma levels do not change with age, the final target dose based on a careful assessment of the patient's clinical response may be similar in healthy younger and older patients.

Maintenance/Continuation/Extended Treatment
There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with SERZONE. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown. Although there are no efficacy data that specifically address maintenance antidepressant treatment with SERZONE, the safety of nefazodone in long-term use is supported by data from both double-blind and open-label trials involving more than 250 patients treated for at least one year.

Switching Patients to or from a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with SERZONE. In addition, at least 7 days should be allowed after stopping SERZONE before starting an MAOI.

HOW SUPPLIED

SERZONE® (nefazodone hydrochloride) tablets are hexagonal tablets imprinted with BMS and the strength (i.e., 100 mg) on one side and the identification code number on the other. The 100 mg and 150 mg tablets are bisect scored on both tablet faces. The 200 mg and 250 mg tablets are unscored.

NDC CODE	*DESCRIPTION*
NDC 0087-0032-31	100 mg white tablet, bottle of 60
NDC 0087-0032-44	100 mg white tablet, blister pack of 100
NDC 0087-0039-31	150 mg peach tablet, bottle of 60
NDC 0087-0039-01	150 mg peach tablet, blister pack of 100
NDC 0087-0033-31	200 mg light yellow tablet, bottle of 60
NDC 0087-0033-44	200 mg light yellow tablet, blister pack of 100
NDC 0087-0041-31	250 mg white tablet, bottle of 60

Store at room temperature, below 40° C (104° F) and dispense in a tight container.

Bristol-Myers Squibb Company
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nputer Patent Annuities
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BRISTOL — MYERS COMPANY
Patent Department (N.Y.)
Received: FEB 03 1986

RISTOL-MYERS
TTN.MS MARY B.STAWASZ
ATENT COUNSEL
45 PARK AVENUE
EW YORK N.Y.10154
.S.A.

1474 Account 78100

OFFICIAL RECEIPT/RENEWAL CERTIFICATE

We enclose the official receipt for the following patent. This document should be kept in a safe place in case proof of renewal is required at any time. If you would like your official receipts kept and stored here in future, please let us know by signing and returning this letter: a fee of £1 for this service would then be added to each future invoice for annuities paid on your account.

Date 25 JAN 8

ry	Patent No.	Due Date	Annuity	Your Reference Patentee
HALF FEES)	4338317	JAN.06	04	MJ0536- MEAD JOHNSON+CO -244464-16MAR81

APPENDIX 3

Computer Patent Annuities

PATENT DESIGN & TRADEMARK RENEWALS WORLDWIDE

R. S. CHANNERY, B.Sc. CPA
R. C. WALKER, MA, CPA

N. WADDLETON, BRD, MA, C.Eng, FIEE, FBIM, CPA
M. F. WHITE, MA, C.Eng, F.I.Mech.E, CPA
W. P. McCALLUM, MITMA, CPA
A. MASSEY, MITMA, CPA
C. R. HAIGH, MA, CPA
D. G. TAYLOR, B.Sc, CPA

G. E. SPENCER, MA, CPA
SHEILA P. LESLEY, MA, MITMA, CPA
J. N. LEACH, B.Sc, MBA, CPA
P. M. GORE, B.Sc, CPA
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M. J. ROOS, CPA

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Computer Patent Annuities Inc.
1 Jefferson Davis Highway
Suite [illegible] Arlington VA 22202

UNITED STATES C/O RCW
COMMISSIONER OF PATENTS
BOX M.FEE
WASHINGTON D.C.20231

PAYOR NUMBER 000197

INSTRUCTION ANWEISUNG

Please maintain the undermentioned cases and forward to us the official renewal certificates as soon as possible.

Veuillez maintenir en vigeur les affaires mentionnees ci-dessous et nous envoyer les certificats de renouvellement aussitot que possible.

Bitte halten Sie die unten bezeichneten Angelegenheiten aufrecht und senden Sie uns die amtlichen Empfangsbescheinigungen moeglichst bald zu.

Account no. 08890

Date 19/12/85

Country	Patent No.	Due Date	Annuity	Applicant / Patentee Serial No. Filing Date	Cost
USA (HALF FEES)	4338317	JAN.06	4	MEAD JOHNSON+CO -244464-16MAR81	225.00
USA (HALF FEES)	4338373	JAN.06	4	MITSUBISHI GAS -217919-18DEC80	225.00
USA (HALF FEES)	4338378	JAN.06	4	DENKI KAGAKU -289091-31JUL81	225.00
USA (HALF FEES)	4338385	JAN.06	4	SUMITOMO METAL -271088-05JUN81	225.00

536

ALL PATENTS DATED July 06, 1982 TOTAL: $3375.00

OUR CHEQUE FOR $3375.00 in payment of the maintenance fees due on the above patents is enclosed herewith. Please stamp and return the enclosed copy of this letter as confirmation of receipt.

Yours faithfully

R. C. Walker

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

3 KC4
J394

PAYOR NUMBER
000197

COMPUTER PATENT ANNUITIES
% COMPUTER PATENT ANNUITIES INCORP.
1111 JEFFERSON DAVIS HIGHWAY
SUITE 514
ARLINGTON, VA 22202

DATE MAILED
01/03/90

088865

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,338,317	171	495	----	06/244,469	07/06/82	03/16/81	08	NO	PAID
2	4,338,366	171	495	----	06/244,567	07/06/82	03/17/81	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	MJ 536
2	2508R2C

DIRECT THE RESPONSE TOGETHER WITH PART B OF THIS NOTICE, AND ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

$ 495.00 — 171

RECORDED

Computer Patent Annuities
Computer Patent Annuities, Inc.
[illegible] Jefferson Davis Highway
Suite [illegible]16
Arlington, VA 22202

Payor Number 000197

December 22, 1989

REEL 234 FRAME 1891

PATENT NO.	SERIAL NO.	PATENT DATE	FILING DATE	AMOUNT
[illegible]142	226090	06 Jul 1982	19 Jan 1981	495.00
4338143	248419	06 Jul 1982	27 Mar 1981	495.00
4338211	252691	06 Jul 1982	09 Apr 1981	495.00
4338245	292118	06 Jul 1982	12 Aug 1981	495.00
4338246	295163	06 Jul 1982	21 Aug 1981	495.00
4338317	244464	06 Jul 1982	16 Mar 1981	495.00
4338366	244567	06 Jul 1982	17 Mar 1981	495.00
4338378	289091	06 Jul 1982	31 Jul 1981	495.00
4338456	235744	06 Jul 1982	18 Feb 1981	495.00
4338467	233148	06 Jul 1982	10 Feb 1981	495.00
4338471	217116	06 Jul 1982	17 Dec 1980	495.00
4338385	271088	06 Jul 1982	05 Jun 1981	495.00
4599712	475542	07 Jul 1986	15 Mar 1983	490.00
4590529	587272	20 May 1986	07 Mar 1984	490.00 120.00
			TOTAL	$14,545.00

Please stamp and return the enclosed copy of this letter as confirmation of receipt of our payment.

Sincerely,

Robert C. Walker

Robert C. Walker

RCW/rk

Enclosures

090 12/27/89 4338317 2 171 495.00 CK

2X5

Computer Patent Annuities

PATENT, DESIGN & TRADE MARK RENEWALS WORLDWIDE
TRADE MARK HEADINGS

PO Box 778 Jersey JE1 1BL Channel Islands

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C.P.A.FROM 1/2/90 NO DIV OR
PCT IN TITLE FIELD SORT CODE
40 OCTOBER 91

Our ref: 504786/OFRCPT

Your ref:

Date: 03 FEB 1994

Dear Sir

Re: Your case detailed below:

Country Name:	U.S.A.
Type Name:	Patent
Client's Reference:	MJ0536-
Patentee:	MEAD JOHNSON+CO
Patent No.:	4338317
Base date:	06 JUL 1982
Client no.:	0859207
Annuity:	3

We enclose the official receipt for the payment of the annuity detailed above. This document should be kept in a safe place in case proof of renewal is required at any time. If you would like your official receipts stored by CPA in future, please let us know by signing and returning this letter: a fee of £1 for this service will then be added to each future invoice for annuities paid on your account.

Yours faithfully,

Computer Patent Annuities

595

RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,338,317	185	2820	----	06/244,464	07/06/82	03/16/81	12	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	MJ 536

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Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
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COMPUTER PATENT ANNUITIES
C/O COMPUTER PATENT ANNUITIES, INC.
1111 JEFFERSON DAVIS HIGHWAY
SUITE 514, CRYSTAL GATEWAY NORTH
ARLINGTON, VA 22202

DATE MAILED
01/10/94

MAINTENANCE FEE STATEMENT

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
10/15/82	Original IND	IND is filed. Includes Protocol 030A2-001.
10/22/82	FDA Letter	FDA acknowledges receipt of the IND and assigns IND #20,993 to it.
12/09/82	FDA Letter	FDA comments and suggestions following review of original IND.
04/19/83	CMC Amendment	Response to FDA's letter of 12/09/82 - Chemistry Section.
06/28/83	Protocol Amendment	Protocol 030A2-0001 is submitted.
06/28/83	Letter to FDA	Copy of U.S.A.N. letter listing "Nefazodone" as designated name for MJ13754.
06/28/83	Information Amendment - Clinical	Updated Basic Data Brochure is submitted.
07/12/83	FDA Letter	FDA comments and suggestions pertaining to 04/19/83 chemistry responses.
11/21/83	Annual Report	Summaries of studies 030A2-001-1509 and 030A2-001-1576.
08/28/84	Protocol Amendment	Protocol 030A2-0002 is submitted.
10/26/84	CMC Amendment	CMC information pertaining to two control agents, 25 mg Imipramine tablets and 25 mg trazadone tablets, is submitted.
11/06/84	Information Amendment - Clinical	Investigator's Report on study 1509 is submitted.
12/05/84	Annual Report	Contains a summary of studies 1509 and 1576 and plans for Protocol 030A2-0002.
01/23/85	Information Amendment - Pharmacology/Toxicology	Report No. JOHN-RE-09241 and Report No. ELRO-SV-09223 is submitted.
05/07/85	Protocol Amendment	Protocol 030A2-0004 is submitted.
05/15/85	Information Amendment - Clinical	Report No. LAND-CL-10576 is submitted.
05/15/85	Protocol Amendment	Protocol 030A2-0006 is submitted.
05/20/85	Protocol Amendment	Protocol 030A2-0005 is submitted.
06/13/85	Information Amendment - Pharmacology/Toxicology	Submission of 4 non-clinical pharmacology reports, 5 toxicology reports and 1 preclinical MAP report.
06/13/85	Information Amendment - Clinical	Clinical Report No. LAND-CL-10576 is re-submitted.

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
08/30/85	FDA Letter	FDA comments on Clinical and Pharmacokinetic data previously submitted and recommendations concerning this data.
10/02/85	General Correspondence	Response to FDA letter of 08/30/85 regarding Clinical and Pharmacokinetic data previously submitted.
10/02/85	CMC Amendment	CMC Amendment containing revised synthesis, specifications and stability of drug substance and CMC pertinent to nefazodone and matching placebo capsules.
10/25/85	Information Amendment - Pharmacology/Toxicology	Report No. HAWK-HC-11023 is submitted.
10/25/85	Information Amendment - Clinical	Interim Clinical Report No. BARO-PE-10833 and Pharmacokinetic Report No. MAYO--RF-11006 are submitted.
11/18/85	Protocol Amendment	Protocol 030A2-0007 is submitted.
12/18/85	Protocol Amendment	Protocol 03A0B-002 is submitted.
01/02/86	FDA Letter	Comments on extension phase for planned studies.
02/27/86	Information Amendment - Clinical	Clinical pharmacology report on study 1885 is submitted (HEIM-LR-11343).
02/27/86	CMC Information	CMC information pertaining to 150 mg capsules is submitted.
02/27/86	Information Amendment - Pharmacology/Toxicology	Seven non-clinical pharmacology reports are submitted.
08/20/86	FDA Letter	FDA comments on the 10/25/85 submission of data on single and multiple dose pharmacokinetic study.
08/29/86	Information Amendment - Pharmacology/Toxicology	Two non-clinical pharmacology and 4 toxicology reports are submitted.
08/29/86	Annual Report	Status reports on all studies and a final report on study 1509 are submitted.
12/10/86	Information Amendment - Clinical	Basic data brochure is updated to include results of Phase II studies.
04/13/87	Protocol Amendment	Protocol 03A0A-004 is submitted.
05/06/87	Protocol Amendment	Protocol 03A0B-003 is submitted.
5/06/87	Information Amendment - Clinical	Report RUSS-JW-11761 is submitted.

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
05/06/87	Information Amendment - CMC	CMC information is submitted for ^{14}C-labeled Nefazodone formulations.
05/08/87	Information Amendment - Clinical	Submission of Preliminary Evidence of Efficacy.
06/03/87	FDA Letter	Regarding long-term extension phase of studies.
06/11/87	Annual Report	Consisting of updated summary of all studies currently filed with the IND.
06/15/87	General Correspondence	Response to FDA letter of 06/03/87.
07/24/87	FDA Letter	Comments regarding our 6/15/87 submission.
08/10/87	Information Amendment - Pharmacology/Toxicology	Three toxicology, 3 non-clinical pharmacology and 1 preclinical MAP reports are submitted.
09/15/87	Protocol Amendment	Protocol 03A8A-001 is submitted.
09/15/87	Information Amendment - CMC	CMC information supporting the use of nefazodone, trazodone, buspirone, and matching placebo capsules.
10/16/87	Protocol Amendment	Protocol 59B6A-001 is submitted.
10/16/87	Information Amendment - Pharmacology/Toxicology	Six non-clinical pharmacology reports are submitted.
10/16/87	Information Amendment - Clinical	Report ROBE-DL-25114, a preliminary report is submitted.
10/26/87	Safety Report	Initial written report.
11/23/87	FDA Letter	Regarding the enrollment of women of child bearing potential.
01/20/88	Annual Report	Contains status report on all clinical studies, pre-clinical and CMC activity.
01/20/88	Information Amendment - Clinical	Basic data brochure is updated with results of Open and Double-Blind Phase II studies.
07/07/88	Protocol Amendment	Protocol CN104-002 is submitted.
07/07/88	Information Amendment - CMC	CMC information in support of imipramine capsules used in clinical trials.
09/14/88	Information Amendment - Pharmacology/Toxicology	Report TAYL-DP-25249 is submitted.
12/14/88	Protocol Amendment	Protocol CN104-006 is submitted.
2/01/89	Annual Report	Includes 15 non-clinical summaries or study reports; three pharmacokinetic reports on studies 2553, 2146 and 2025; two clinical reports on studies 2025 and 2553; seven publications; ten published abstracts.

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
02/13/89	Protocol Amendment	Protocol CN104-005 is submitted.
09/29/89	Protocol Amendment	Protocol CN104-009 is submitted.
09/29/89	Information Amendment - Clinical	Updated basic data brochure is submitted. Contains results of open and double-blind Phase II studies.
10/04/89	Protocol Amendment	Protocol CN104-011 is submitted.
10/04/89	Information Amendment - CMC	CMC information in support of fluoxetine capsules used in clinical trials.
10/15/89	Information Amendment - Pharmacology/Toxicology	Report TAYL-DP-09224 - Pharmacology Summary is submitted.
11/07/89	Protocol Amendment	Protocol CN104-021 is submitted.
11/28/89	Information Amendment - CMC	CMC information in support of dextroamphetamine capsules and diazepam capsules to be used in clinical studies.
11/28/89	Protocol Amendment	Protocol CN104-015 is submitted.
11/28/89	Protocol Amendment	Protocol CN104-025 is submitted.
11/28/89	Protocol Amendment	Protocol CN104-023 is submitted.
11/28/89	Protocol Amendment	Protocol CN104-013 is submitted.
12/15/89	Information Amendment - CMC	CMC information in support of an oral nefazodone solution.
12/20/89	Information Amendment - Pharmacology/Toxicology	Report BRAS-JP-25416 is submitted.
01/10/90	Protocol Amendment	Protocol CN104-030 is submitted.
01/12/90	Information Amendment - CMC	CMC information supporting the use of cimetidine tablets in clinical trials.
01/18/90	Protocol Amendment	Protocol CN104-022 is submitted.
01/26/90	Protocol Amendment	Protocol CN104-017 is submitted.
3/13/90	FDA Meeting	End-of-Phase II meeting
03/22/90	Information Amendment - Pharmacology/Toxicology	Two non-clinical pharmacology study reports are submitted.
03/30/90	Information Amendment - Pharmacology/Toxicology	Report GEIS-MA-25360 is submitted.
03/30/90	Annual Report	Status report on all studies currently open under this IND along with summaries of pre-clinical and CMC activity.
07/15/90	Protocol Amendment	Protocol CN104-038 is submitted.

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
07/26/90	Safety Report	Initial written report.
08/17/90	Information Amendment - CMC	CMC information supporting drug substance; alternative manufacturing facilities for drug substance and drug products.
08/29/90	Protocol Amendment	Protocol CN104-035 is submitted.
09/20/90	Information Amendment - CMC	CMC information in support of the use of triazolam and haloperidol capsules in clinical studies.
09/20/90	Protocol Amendment	Protocol CN104-036 is submitted.
10/08/90	General Correspondence	Draft protocols CN104-043 and CN104-047 are submitted.
10/08/90	Protocol Amendment	Protocol CN104-037 is submitted.
10/24/90	Safety Report	Follow-up report.
10/30/90	Information Amendment - CMC	CMC information pertaining to the manufacture of deuterated nefazodone.
10/30/90	Protocol Amendment	Protocol CN104-043 (Finalized) is submitted.
11/07/90	General Correspondence	Request for a Pre-NDA meeting with the Agency.
11/12/90	Information Amendment - CMC	Response to an FDA request for dissolution data.
11/27/90	Information Amendment - CMC	CMC information pertaining to the D_7-nefazodone for protocol CN104-047.
11/27/90	Protocol Amendment	Protocol CN104-047 (Finalized) is submitted.
01/03/91	Protocol Amendment	Protocol CN104-040 is submitted.
01/28/91	Protocol Amendment	Protocol CN104-053 is submitted.
02/07/91	Annual Report	Annual report is submitted.
2/11/91	FDA Meeting	Pre-NDA meeting
03/27/91	FDA Meeting	CMC Pre-NDA meeting
05/22/91	Protocol Amendment	Protocol CN104-903 is submitted.
06/26/91	Information Amendment - CMC	CMC Information providing for alternative packaging components; alternative packaging site; updated stability data; and CMC information pertaining to digoxin capsules and placebo tablets.
06/26/91	Protocol Amendment	Protocol CN104-057 is submitted.
06/28/91	Protocol Amendment	Protocol CN104-045 is submitted.
07/01/91	Protocol Amendment	Protocol CN104-058 is submitted.
08/05/91	Protocol Amendment	Protocol CN104-068 is submitted.

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
09/06/91	NDA	NDA is submitted- #20-152.
09/18/91	Protocol Amendment	Protocol CN104-054 is submitted.
10/08/91	Protocol Amendment	Protocol CN104-063 is submitted.
11/05/91	Protocol Amendment	Protocol CN104-069 is submitted.
11/06/91	Information Amendment - CMC	CMC Information: Revised synthesis of nefazodone drug substances; additional drug substance manufacturing site; placebo capsules; and alprazolam capsules.
11/19/91	Protocol Amendment	Protocol CN104-074 is submitted.
11/19/91	Protocol Amendment	Protocol CN104-056 is submitted.
12/02/91	Protocol Amendment	Protocol CN104-082 is submitted.
12/17/91	Information Amendment - Clinical	Updated Investigators Brochure incorporating overview of clinical findings from the NDA.
01/03/92	Protocol Amendment	Protocol CN104-081 is submitted.
01/17/92	Information Amendment - CMC	CMC information on lorazepam capsules and updated specifications for nefazodone drug substance.
02/18/92	Protocol Amendment	Protocol CN104-080 is submitted.
02/18/92	Protocol Amendment	Protocol CN104-076 is submitted.
03/17/92	Information Amendment - CMC	CMC Information on warfarin tablets.
03/17/92	Protocol Amendment	Protocol CN104-066 is submitted.
04/06/92	Protocol Amendment	Protocol CN104-075 is submitted.
04/24/92	Protocol Amendment	Protocol CN104-078 is submitted.
05/28/92	Annual Report	Annual Report is submitted.
09/15/92	Protocol Amendment	Protocol CN104-087 is submitted.
09/15/92	Protocol Amendment	Protocol CN104-064 is submitted.
09/22/92	Information Amendment - Clinical	Updated Investigators Brochure is submitted.
10/06/92	Protocol Amendment	Protocol CN104-077 is submitted.
10/09/92	Safety Report	Initial written report.
10/09/92	Information Amendment - Clinical	Addendum #4 to the Investigators Brochure.
10/26/92	Protocol Amendment	Protocol CN104-083 is submitted.
11/05/92	Protocol Amendment	Protocol CN104-101 is submitted.

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
11/17/92	Information Amendment - Pharmacology/Toxicology	One non-clinical pharmacology study report, 1 toxicology study report and 8 pre-clinical MAP study reports are submitted.
12/18/92	Information Amendment - CMC	Updated CMC information on drug substance and drug products; additional manufacturing site for drug substance and drug product.
01/13/93	Annual Report	Annual Report is submitted.
02/05/93	Protocol Amendment	Protocol CN104-092 is submitted.
02/19/93	Protocol Amendment	Protocol CN104-113 is submitted.
02/19/93	Protocol Amendment	Protocol CN104-110 is submitted.
02/19/93	Protocol Amendment	Protocol CN104-111 is submitted.
02/19/93	Information Amendment - CMC	CMC information on sertraline capsules to be used in clinical trials.
03/05/93	Protocol Amendment	Protocol CN104-115 is submitted.
03/08/93	Information Amendment - CMC	CMC information for nefazodone tablets and an additional packaging and labeling facility.
03/23/93	Protocol Amendment	Protocol CN104-104 is submitted.
03/23/93	Protocol Amendment	Protocol CN104-103 is submitted.
03/26/93	Protocol Amendment	Protocol CN104-088 is submitted.
04/02/93	Protocol Amendment	Protocol CN104-106 is submitted.
04/13/93	Protocol Amendment	Protocol CN104-105 is submitted.
04/13/93	Protocol Amendment	Protocol CN104-109 is submitted.
04/23/93	Protocol Amendment	Protocol CN104-114 is submitted.
05/07/93	Information Amendment - CMC	CMC information on imipramine capsules and an additional packaging site for clinical supplies.
07/23/93	Protocol Amendment	Protocol CN104-100 is submitted.
08/02/93	Safety Report	Initail written report.
08/06/93	Protocol Amendment	Protocol CN104-121 is submitted.
08/19/93	CMC Amendment	A new packaging site for nefazodone hydrochloride tablets is identified.
10/21/93	Protocol Amendment	Protocol CN104-119 is submitted.
01/28/94	Annual Report	Status report of investigations conducted under this IND for the period from 6/16/92 through 11/14/93.

IND 20993 - NEFAZODONE HCl CHRONOLOGY OF POST-IND COMMUNICATIONS		
DATE	**TYPE OF CONTACT**	**SUMMARY**
03/04/94	Protocol Amendment	Protocol CN104-127 is submitted.
07/07/94	CMC Amendment	New positive control product for upcoming clinical trials.
07/25/94	Information Amendment-Toxicology	Non-clinical Report: Antigenicity Study in Guinea Pigs and Mice.
09/02/94	Protocol Amendment	Protocol CN104-029 is submitted.

NDA 20-152 SERZONE® (Nefazodone HCl) Tablets Chronology for Patent Term Extension		
Date	**Type of Contact**	**Summary / Description**
9/6/91	**Submission #001**	Original NDA is submitted **(Volumes 1.1 - 1.277)**
9/11/91	FDA Letter	Acknowledges receipt of NDA
9/20/91	FDA Letter	Acknowledges receipt of NDA and corrects "filing" date. If acceptable, **"Filing date will be 11/6/91".**
11/5/91	**Submission #002**	Expanded Table of Contents for the entire NDA is submitted, as requested.
11/15/91	**Submission #003**	Request for a meeting to discuss our proposals and present prototypes of the computer systems we will provide for the electronic submission of portions of the NDA.
1/7/92	FDA Letter	FDA letter requesting reanalysis of certain placebo-controlled studies.
1/17/92	**Submission No.004**	First Safety Update is submitted
1/21/92	**Submission No.005**	Agenda for 1/30/92 meeting regarding the demonstration of the computer systems prototypes for the electronic submission of portions of the NDA.
1/30/92	FDA Meeting	Presentation of the prototypes of the computer systems for Document Review (WP5.1) and Image Review (CRFs) that will be loaned to the Division.
2/14/92	FDA Meeting	Installation of Case Report Forms from Safety Update No. 1 to the Image Review Computer System.
2/20/92	**Submission No. 006**	Tumor data from carcinogenicity studies are submitted in response to a 1/31/92 request from the Agency.
2/26/92	**Submission No. 007**	Response to the 1/7/92 letter requesting additional statistical analyses.
2/27/92	**Submission No. 008**	Replacement pages for 2 appendices for the final study report for Protocol CN104-005.
3/16/92	**Submission #009**	Replacement pages for integrated safety summary (Volume 1.188).
3/18/92	**Submission #010**	WP5.1 documents on diskette of NDA section 6 (Human Biopharmaceutics) reports and summaries for the Biopharmaceutics reviewer(s).
3/31/92	**Submission #012**	CMC Amendment - Revised Environmental Assessment Report.
4/3/92	**Submission #011**	Amendment No. 3 to Report LEMA-P-12909 to correct for errors found while preparing the electronic data for submission (Submission No. 006).
4/15/92	**Submission #013**	Proposal for submission of individual displays of safety data as electronic images.
4/30/92	**Submission #014**	Response to request for dose and duration of treatment displays.

NDA 20-152 SERZONE® (Nefazodone HCl) Tablets Chronology for Patent Term Extension		
Date	**Type of Contact**	**Summary / Description**
5/12/92	Submission #015	Issues and list of Attendees for the scheduled teleconference to discuss our 2/27/92 response to the 1/7/92 FDA letter.
6/11/92	Submission #016	Post-Hoc exploratory analysis results for Protocol CN104-005.
6/18/92	FDA Teleconference	Discussion of our 2/27/92 (Submission No. 007) response to the Agency's request for Re-Analysis of several Placebo-Controlled Trials (1/7/92 letter) and our proposal for the electronic submission of the individual safety data displays (Submission #13).
6/29/92	Submission #017	Minutes of teleconference of 6/18/92
7/20/92	FDA Letter	Fax draft of CMC deficiency Letter
8/13/92	Submission #018	Individual Safety Data Displays are submitted.
8/18/92	Submission #019	Graphs of the primary efficacy variables for subcenters in studies conducted under Protocols CN104-005, CN104-002-001 and 03A0A-004A-2407.
8/25/92	FDA Letter	Regarding 7/20/92 FAX of CMC deficiency letter.
9/2/92	Teleconference	To discuss the completion (format and content) of the requested safety table templates provided on 9/1.
9/4/92	FAX	Minutes of teleconference of 9/2/92.
10/1/92	Submission #020	Copies of additional CRF pages found missing from the NDA paper copy during the Image Review Computer System QA review.
10/16/92	Submission #021	Submission of completed safety table templates (9/1/92 request).
10/23/92	Submission #022	Printed copies & WP5.1 Diskette of revised safety table templates as requested.
11/18/92	Submission #023	Response to the 7/17/92 CMC review letter and submission of a modified NDS synthesis and NDS manufacturing site.
12/8/92	Submission #024	Descriptive dataset information for 2 placebo-controlled trials for use by the statistical reviewer.
12/16/92	Submission #025	Additional (11/6/92 request) and revised (9/1/92 request) Safety Table Templates.
2/9/93	Submission #026	Revised descriptive dataset information for 2 placebo-controlled trials for use by the statistical reviewer.
3/4/93	Submission #027	Submission of WP5.1 documents - Requested Table of All Studies; Table of Controlled Studies; 5 Key Study Summaries; Efficacy Data Tables; Nefazodone Safety Tables Update
3/16/93	FAX from FDA	Requesting Clarification Regarding Cutoff Dates; Enumerating Patients from Crossover Studies; and Patient Exposure Years.

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Date	**Type of Contact**	**Summary / Description**
3/29/93	**Submission #028**	The following summary tables are submitted: (A) Overview of Efficacy Trials (B) Important Clinical Issues (B-1) Anxiety as a Predictor of Response (B-2) Efficacy of Nefazodone in the Long-Term Treatment of Depression Report (B-3) Nefazodone Overview of Clinical Findings, and (B-4) Nefazodone Summary of Safety Information from Elderly Patients and Subjects
3/30/93	**Submission #029**	A request for a teleconference to discuss issues related to the submission of additional safety data and the scheduling of the Advisory Committee meeting.
4/7/93	**Submission #030**	Response to the 3/16 Fax.
4/19/93	**Submission #032**	Final study reports on studies CN104-053-001 and CN104-068-001 are submitted.
4/23/93	**Submission #031**	Patient exposure data for all treatment groups and suicide liability rates for these treatment groups using PEY calculations based on exposure as of Safety Update No. 1.
4/27/93	**Submission #033**	Adaptation Table is submitted in response to a 3/29 request.
4/30/93	**Submission #034**	Response to a request for "short position papers" on the following safety-related topics: Withdrawal Phenomena and Abuse Potential; Human Reproductive Data; Overdose; Drug-Demographic, Drug-Disease and Drug-Drug Interactions.
5/7/93	**Submission #035**	Submission of the Proprietary Name - "Serzone™"
5/10/93	**Submission #036**	Patient exposure data for all treatment groups and suicide liability rates for these treatment groups using PEY calculations based on exposure as of 4/15/93.
5/10/93	**Submission #037**	Submission of copies of the Word Perfect 5.1 files of the biopharmaceutics reports included in the original NDA.
5/12/93	**Submission #038**	Information on the impact on the rate of patient discontinuation of an amendment to Protocol CN104-005 which modified the recommended dosing regimen to discourage rapid runs up to the maximum dose.
5/18/93	**Submission #039**	Additional statistical analyses and appendices for Protocol CN104-005.
5/20/93	**Submission #040**	A revised Environmental Assessment report.
5/25/93	**Submission #041**	To provide a desk copy of the dissolution data submitted in the NDA.
5/25/93	**Submission #042**	Provides a proposal for Safety Update No. 2.
5/25/93	**Submission #043**	Table of the demographic information and a summary table of the pharmacokinetic parameters for specific studies submitted.

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Date	**Type of Contact**	**Summary / Description**
5/26/93	Submission #044	Revisions to the 1% AE table in the Safety Table Templates to adjust percentages for gender.
5/27/93	Submission #045	Demographic information and a summary table of the pharmacokinetic parameters for Study CN104-053.
5/28/93	Submission #046	Submission of a revised table of "Other Events" (Package Insert) and a table of the "Incidence of AE That Led to Discontinuation in Patients Who Discontinued Due to AE, in Open and Double-Blind Trials" that combined both short-term and long-term experience.
6/2/93	Fax from FDA	Request for justification of the doses used in Segment II rabbit study.
6/3/93	Submission #047	Submission of reports on MAP studies, clinical pharmacology studies, and a pre-clinical study, all in support of revised labeling.
6/3/93	Submission #048	Revised draft labeling is submitted.
6/4/93	Submission #049	Submission of revised table of "Other Events Observed During the Premarketing Evaluation" (draft labeling). Correction to Submission No. 46.
6/4/93	Submission #050	Electronic SAS datasets on diskette and printed copies of the supporting documentation for three of our placebo-controlled studies.
6/7/93	Teleconference	To discuss our key efficacy trials.
6/8/93	Submission #051	Response to questions raised in the 5/26 FAX.
6/15/93	Submission #052	Revised and/or new safety tables requested.
6/16/93	Submission #053	Justification of the high-dose used in the Segment II rabbit study.
6/17/93	Submission #054	Submission of comparison of the pharmacologic properties of nefazodone and its principal metabolites.
6/18/93	Submission #055	Response to 6/15 request for additional tables.
6/21/93	Submission #056	Additional information concerning Study 2146 is submitted.
6/21/93	Submission #057	Summary of Postural Hypotension in Nefazodone-Treated Patients is submitted.
6/22/93	Submission #058	Exploratory Age/Gender Safety and Efficacy Analyses and Race Efficacy Analyses.
6/24/93	Submission #059	Electronic SAS datasets for Protocol CN104-005.
6/25/93	Submission #060	Electronic data set in ASCII format for Protocol 030A2-0002.
6/28/93	Submission #061	Table of PK and pharmacologic profile of Nefazodone and its metabolites and the final study report for Protocol CN104-038.

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Date	**Type of Contact**	**Summary / Description**
6/28/93	Submission #062	Status of the review of worldwide marketing applications; summary tables of the pharmacology and pharmacokinetics of nefazodone and its metabolites; revised table of All Studies.
6/29/93	Submission #063	Background information for upcoming Advisory Committee Meeting.
6/30/93	Submission #064	Submission of additional safety information.
7/2/93	Submission #065	BMS position regarding confidentiality of information submitted for the Advisory Committee Meeting.
7/2/93	Submission #066	Additional ANCOVA and CMH analyses for Study 03A0A-003-2191 and Protocol 03A0A-004B.
7/2/93	Submission #067	Electronic data sets containing mean plasma concentration data for nefazodone and its metabolites from Protocol CN104-021.
7/7/93	Submission #068	SAS dataset for Protocol CN104-006.
7/9/93	Submission #069 & FAX	Additional safety information pertaining to certain ECG, clinical laboratory and vital signs measurements.
7/12/93	Submission #070	ANCOVA results for Study CN104-001-001.
7/15/93	Submission #071	Copies of the slides BMS intends to present at the Advisory Committee Meeting on 7/19/93.
7/19/93	Meeting	NDA 20-152 is presented to the Psychopharmacologic Drugs Advisory Committee.
7/21/93	Submission #072	Additional slides presented at the Advisory Committee Meeting are submitted.
8/6/93	Submission #073	Additional efficacy tables and a list of non-IND studies.
8/6/93	Submission #074	CMC and clinical rationale for adding 150 and 250 mg tablets to the NDA.
8/6/93	Submission #075	SAS data sets for six placebo-controlled studies.
8/17/93	FDA Teleconference	With the NDA biopharmaceutics reviewers to discuss issues which arose during the Advisory Committee and their review of this NDA.
8/25/93	Submission #076	Draft container labels for Serzone Tablets are submitted.
9/1/93	Submission #077	Official submission of the minutes of the teleconference held on 8/17/93.
9/9/93	Submission #078	Information requested in teleconference of 8/17/93 is submitted.
9/10/93	Submission #079	A draft "Summary Basis of Approval" (SBA) is submitted.
9/16/93	Submission #080	Information on the nefazodone hydrochloride drug substance packaging material.

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Date	**Type of Contact**	**Summary / Description**
9/22/93	**Submission #081**	Stability data and batch analysis data on batches of Serzone Tablets manufactured with drug substance from Humacao, Puerto Rico facility are submitted.
9/29/93	**Submission #082**	Summaries for three biopharm studies, using the format contained in the 9/7/93 FAX are submitted.
10/1/93	**Submission #083**	Brief summaries of the three remaining placebo-controlled trials that were not included in Submission No. 027. (030A2-0004/0005; 03A0A-004A; CN104-006)
10/6/93	**Submission #084**	Drug Substance synthesis update.
10/14/93	**Submission #085**	Response to the 9/17 FAX of CMC deficiencies.
10/20/93	**Submission #086**	Worldwide Regulatory status of nefazodone.
10/26/93	**Submission #087**	Worldwide Literature update.
10/27/93	**Submission #088**	Chronology of submissions to this NDA through Safety Update No. 2.
10/28/93	**Submission #089**	Safety Update No. 2 is submitted.
11/17/93	**Submission #090**	Revised draft labelling to incorporate information from Safety Update No. 2.
01/04/94	**Submission #091**	Response to 12/16 request for updated batch analysis data on Serzone 150 mg and 250 mg tablets.
01/12/94	**Submission #92**	Revised Draft Labeling & Drug Interaction Study Reports for Study No. CN104-078-001 and Study No. CN104-057-001.
2/17/94	**Submission #093**	Response to a request for a Certificate of Analysis for a New Drug Substance batch made at Humacao.
3/16/94	**Submission #094**	FOI-Releasable Environmental Assessment Report and response to reviewer's 3/4 request for additional information.
3/24/94	**Submission #095**	Additional information pertaining to the FOI-Releasable Environmental Assessment Report.
05/12/94	**Submission #096**	CMC Amendment - Bottle and blister labels for SERZONE tablets.
11/07/94	**FDA Letter**	FDA has completed its review and has concluded that the application is APPROVABLE.
11/19/94	**Submission #097**	Notification of Intent to Amend
11/17/94	**Submission #098**	B-MS response to Approvable Letter (2 Volumes 98.1 / 98.2.
11/22/94	**Submission #099**	CMC Amendment - B-MS response to FDA recommendation for revision of dissolution method.
11/23/94	**Submission #100**	Proposed Draft Labeling- Response to Approvable Letter.
11/28/94	**Submission #101**	Response to FDA Request- Worldwide Literature Update.

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Date	**Type of Contact**	**Summary / Description**
11/28/94	**Submission #102**	Response to FDA Request - Worldwide Regulatory Status.
12/06/94	**Submission #103**	Response to FDA Request - Documentation for labeling revisions that affect the "safety" information in the insert.
12/08/94	**FDA Meeting**	Discussion of proposed labeling.
12/16/94	**Submission #104**	CMC - Response to CMC issues addressed in approvable letter.
12/22/94	**FDA Letter**	APPROVAL LETTER AND LABELING